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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,487	02/10/2004	Denise L. Faustman	00786/457003	1044

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EXAMINER	
SKELDING, ZACHARY S	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/775,487	FAUSTMAN ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-82* is/are pending in the application.

4a) Of the above claim(s) *78,81 and 82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76,77,79 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2-10-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of species, without traverse, of September 29, 2006 has been entered.

   Claims 1-75 are canceled.

   Claims 76-82 are pending.

2. Applicant's election of the species "diabetes", without traverse, in the reply filed September 29, 2006 is acknowledged.

   Claims 76, 77, 79 and 80 are under examination as they read on a method for treating an autoimmune disease, wherein the species of autoimmune disease is "diabetes", with TNF-α.

   Claims 78, 81 and 82 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being directed to a non-elected invention.

3. The oath or declaration filed February 10, 2004 is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

   The oath or declaration is defective because:

   Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

   Appropriate correction is required.

4. Claims 76, 79 and 80, given their broadest reasonable interpretation consistent with the instant specification, appear to be supported under 35 U.S.C. § 112, 1st paragraph by the earlier filed applications listed in applicant's claim to the benefit of priority.

   However, claim 77 does **not** appear to be supported under 35 U.S.C. § 112, 1st paragraph by the earlier filed applications listed in applicant's claim to the benefit of priority **(see new matter rejection below)**.

   If applicant disagrees, applicant should present a detailed analysis as to why claim 77 has clear support in an/the earlier filed application(s).

   Accordingly, the effective filing date of claims 76, 79 and 80 is the filing date of USSN 09/031,629, February 27, 1998.

   Moreover, the effective filing date of claim 77 is the same as the filing date of the instant application, February 10, 2004.

5. The IDS filed February 10, 2004 has been considered.

6. Applicant should amend the first line of the specification to update the status of the priority documents.

7. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

   Each letter of trademarked terms should be capitalized wherever it appears and each trademarked term should be accompanied by the generic terminology, e.g., ™ or ®. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

   The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   > The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 77 is rejected under **35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

   Claim 77 was first presented by applicant in the preliminary amendment of May 11, 2005. In this amendment applicant indicated support for claim 77 in priority application USSN 09/031,629. It is noted that applicant indicated where support can be found by reference to particular paragraph numbers; however 09/031,629 as filed does not appear to have been filed with paragraph numbers nor was it pre-grant published. Therefore, in order for all parties to be on the same page, the rejection that follows will refer to page and paragraphs from USSN 09/031,629 as filed.

   Applicant indicates that claim 77 (and base claim 76), find support in USSN 09/031,629 at page 4, 2nd paragraph, page 6, 1st paragraph, paragraph bridging pages 25-26 to second paragraph on page 26 and page 28, 3rd-4th paragraphs.

However, the passages pointed to in support of the instant claims do **not** provide a sufficient written description for claims drawn to a method of treating ***generic*** autoimmune disease, or ***generic*** diabetes, ***with TNF-α.***

The specification does not provide sufficient blazemarks nor direction for the use of TNF-α to treat ***generic*** autoimmune disease, or ***generic*** diabetes. The instantly claimed method, which was not clearly disclosed in the specification as-filed, broadens the scope of the instant disclosure as-filed and introduces a new concept, which violates the written description requirement of the first paragraph of 35 U.S.C. 112.

For example, applicant points to page 4, 2nd paragraph, page 6, 1st paragraph of USSN 09/031,629, which disclose that TNF-α activates NFκB, but does **not** indicate that ***TNF-α*** can be administered to treat ***generic*** autoimmune disease or ***generic*** diabetes. Moreover, applicant points to the paragraph bridging pages 25-26 to second paragraph on page 26 and page 28, 3rd-4th paragraphs of USSN 09/031,629, however these passages relate to "a method of treating autoimmunity by restoring proteolytic processing", thus they relate to a ***particular species*** of autoimmune diseases, i.e., ***those autoimmune diseases that can be treated by restoring proteolytic processing.*** Moreover, these passages do not teach or suggest the use of ***TNF-α*** to restore proteolytic processing.

In contrast, USSN 09/031,629 ***does*** provide sufficient ***written description*** support for claims that recite the administration of TNF-α to treat ***particular species of autoimmune diseases.*** For example ***claim 43 as originally filed*** (now canceled) was directed to autoimmune disease in which TNF-α is administered to treat autoimmune disease "in an amount and for a time sufficient to result in normal NFκB activity in said mammal," wherein according to the specification of USSN 09/031,629, "normal NFκB activity may not exceed 100% of NFκB basal state activity." (see USSN 09/031,629, page 17, 7th paragraph to page 18, 2nd paragraph).

Therefore, claim 43 as originally filed was limited to a method of administering TNF-α to the species of autoimmune patients that specifically have a decreased level of NFκB activity.

Similarly, claims 51 and 59 as originally filed (now canceled) were also limited to methods of administering TNF-α to the species of autoimmune patients that are "suffering from said autoimmune disease resulting from a reduction in NFκB", wherein the treatment results in "normal lymphocyte maturation" (claim 51) or "normal survival" (claim 59).

Thus, the methods of treatment involving administration of TNF-α disclosed in USSN 09/031,629 encompass treating only those ***particular species*** of autoimmune patients who need **increased** NFκB activity **AND** wherein administration of TNF-α either "results in normal NFκB activity" (claim 43) OR "results in normal lymphocyte maturation" (claim 51) OR "restores the cell cycle...and results in normal survival of cells of a tissue" (claim 59).

Moreover, USSN 09/031,629 discloses at page 7, 5th-6th paragraphs, that anti-inflammatory drugs which **decrease** NFκB activity are widely used to treat autoimmune diseases and that NFκB **inhibitioin** is useful in treating the molecular events that lead to diabetes.

Therefore, an ordinary artisan clearly could ***not*** predict the operability of administering TNF-α to treat ***generic*** autoimmune disease or ***generic*** diabetes from the disclosudre of USSN 09/031,629 because according to USSN 09/031,629 some species of autoimmune patients need ***less*** NFκB and therefore would **not** benefit from TNF-α administration.

In other words, the disclosure of USSN 09/031,629 that encompasses administration of TNF-α to a ***particular species*** of autoimmune patients who have ***less than normal basal levels of*** NFκB activity and therefore need ***more*** NFκB activity does ***not*** teach or suggest to the skilled artisan that they should extend the administration of TNF-α to treat ***generic*** autoimmune disease or ***generic*** diabetes since the prior art teaches that other autoimmune patients, including diabetes patients, benefit from treatment with medicines that ***diminish*** NFκB activity.

Note that the **disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if** the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615. "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... **the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed**." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). **See M.P.E.P. § 2163.05 (emphasis added).**

The disclosure of a method of administering TNF-α to treat a particular ***species*** of autoimmune disease (including a particular species of diabetes) does not demonstrate possession of the broader method of administering TNF-α to treat ***generic*** autoimmune disease or ***generic*** diabetes.

Applicant is required to cancel the new matter in the response to this Office Action, or point out where the instant specification provides sufficient written support for claim 77. See MPEP 714.02 and 2163.06.

Alternatively, Applicant is invited to amend the instant claim such that it includes all the limitations encompassed by any one of claims 43, 51 or 59 as originally filed with the instant application.

10. **Claims 76, 77, 79 and 80 are rejected under 35 U.S.C. 112, first paragraph,** as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims, given their broadest reasonable interpretation consistent with the instant specification read on methods of treating ***any*** autoimmune disease by administering TNFα.

The instant specification discloses that mice bred to be non-obese and diabetic (NOD) have a defect in the proteolytic activity that is required for NFκB activation and that factors known to increase NFκB activation, such as TNF-α, could be used to treat diabetes and other autoimmune diseases (see instant specification, in particular, page 21, 4th-7th paragraphs and pages 129-130).

However, the instant specification does not provide sufficient direction or guidance for one of ordinary skill in the art to treat any autoimmune disease in a mammal by administering TNF-α. Indeed, the art prior to applicant's earliest claimed priority date demonstrated that TNF-α ***inhibitors*** are useful in treating human disease and that the level of TNF-α expression is correlated with autoimmune disease severity.

For example, with respect to diabetes in particular, Corbett et al. (Proc Natl Acad Sci U S A. 1993 Mar 1;90(5):1731-5) teaches that TNF-α potentiates the IL-1 + IFN-γ induced production of nitric oxide, a molecule which participates in the beta-cell dysfunction associated with insulin-dependent diabetes mellitus (see entire document, in particular Abstract and pages 1731-1732).

Moreover, with respect to autoimmune disease in general, the prior art teaches that the amount of TNF-α in a patient correlates with the extent of inflammation, and that ***inhibition*** of TNF-α has been used to successfully treat human autoimmune diseases. For example, Marriott BJ (Expert Opin Investig Drugs. 1997 Aug;6(8):1105-8) teaches that TNF-α inhibitors have been used to successfully treat rheumatoid arthritis and Crohn's disease in human clinical trials (see entire document, in particular abstract and pages 1105-1106). Moreover, Altomonte et al. (Clin Rheumatol. 1992 Jun;11(2):202-5) demonstrate that the amount of TNF-α in a rheumatoid arthritis patient's serum is correlated with the degree of inflammation, and TNF-α levels are higher in patients with clinically active disease (see entire document, in particular Abstract and Discussion pages 203-204). Furthermore,

In conclusion, the teachings of the instant specification do not enable the skilled artisan to use TNF-α to treat any autoimmune disease, and based upon the teaching in the art undue experimentation would be required of the skilled artisan to treat autoimmune disease with TNF-α because for many diseases the art teaches this would only serve to exacerbate symptoms.

Furthermore, regarding in vivo methods which rely on generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of

the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

Further, in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Undue experimentation would be required to produce the claimed invention commensurate with the scope of the claims from the written disclosure alone. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims **76, 77, 79 and 80 are rejected under 35 U.S.C. § 102(b)** as anticipated by Satoh et al. (US 5,560,908) as evidenced by Hsu et al. (Cell. 1996 Jan 26;84(2):299-308) (see entire documents).

Satoh teaches a method of treating a mammal, in particular a human, having an autoimmune disease, in particular diabetes, comprising administering a therapeutically effective amount of TNF-α (see entire document, in particular claims 7-9 and columns 3-5).

TNF-α inherently stimulates a signaling pathway that activates NFκB as evidenced by Hsu (see entire document, in particular Introduction and figure 9).

Therefore, the teachings of Satoh, as evidenced by Hsu, anticipate the claimed invention.

13. Claims **76, 77, 79 and 80 are rejected under 35 U.S.C. § 102(e)** as anticipated by Faustman, D (U.S. Patent No. 6,660,487)(see entire document).

Faustman teaches a method of treating a mammal, in particular a human, having an autoimmune disease, in particular diabetes, comprising administering a therapeutically effective amount of TNF-α (see entire document, in particular claim 9 and columns 6-12). Faustman further teaches that TNF-α stimulates a signaling pathway that activates NFκB (see, in particular columns 27-28, example 6).

Therefore, the teachings of Faustman anticipate the claimed invention.

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 76, 77, 79 and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 6,660,487. Although the conflicting claims are not identical, they are not patentably distinct from each other because one of ordinary skill in the art recognizes that by increasing the number of, or maintaining, functional cells of a predetermined type, such as human islet cells, in a mammal having an autoimmune disease said autoimmune disease, such as diabetes, is being treated.

Therefore, the reference claim anticipates the instant claims.

16. Claims 76, 77, 79 and 80 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-30, 65-73 and 91-108 of copending USSN 10/851,983. Although the conflicting claims are not identical, they are not patentably distinct from each other because one of ordinary skill in the art recognizes that by increasing the number of, or maintaining, functional cells of a predetermined type, such as human islet cells, in a mammal having an autoimmune disease said autoimmune disease, such as diabetes, is being treated.

    Moreover, while some claims of USSN 10/851,983 recite administration of a "TNF-α agonists", without specifying administration of TNF-α, *per se*, the USSN 10/851,983 specification defines "TNF-alpha-including therapies" as including "TNF-α".

    Therefore, the reference claims anticipate the instant claims.

    This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 76, 79 and 80 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 41-52 and 82-90 of copending USSN 10/851,983. Although the conflicting claims are not identical, they are not patentably distinct from each other because one of ordinary skill in the art recognizes that by increasing the number of, or maintaining, functional cells of a predetermined type, such as human islet cells, in a mammal having an autoimmune disease said autoimmune disease, such as diabetes, is being treated.

    Therefore, the reference claims anticipate the instant claims.

    This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
December 5, 2006

PHILLIP GAMBEL, PH.D
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12/11/2006